I. Remarks

After entry of the amendment, claims 105-120 and 144-163 are pending.

New claims 152-163 are supported by the originally filed claims and the specification at, for example, page 28, lines 24 through page 29, line 14; page 23, line 26; page 29, line 8; and example 5 on page 33, lines 22-29.

Claims 106, 144, 146, 148 and 150 have been amended to more clearly define the invention.

No issues of new matter should arise and entry of the amendment is respectfully requested.

II. Rejection under 35 USC § 112, First Paragraph: Written Description

Claim 120 is rejected for broadening the scope of the invention as originally filed.

Applicant respectfully traverses the rejection because claim 120 does not broaden the scope of the invention as originally filed. The current specification is exactly the same as the specification that was filed September 29, 2000, and claim 120 is commensurate in scope with the originally filed application. For example, the specification at page 2, lines 4-6 states:

> The present invention is based on the discovery that the use of at least one chemotherapeutic agent and at least one immunoconjugate produces unexpectedly superior results in the treatment of cancer.

Moreover, the specification from page 17, line 3 to page 19, line 3 describes several operative embodiments of representative antibodies that can be conjugated with maytansinoid and used with taxane compounds to produce unexpected superior results. As the PTO correctly points out, Applicant has further provided working examples in support of the teachings in the specification.

Unexpectedly superior results is the same as synergistic results and is the same as greater than additive results. The meaning of the term "unexpectedly superior" is defined in the specification. The specification at page 33, line 29 states that "unexpectedly superior" refers to "synergistic" effects. The results in Figures 5-10 also clearly demonstrate to one of ordinary skill in the art that Applicant is referring to "synergistic" effects as synonymous with "unexpectedly superior" effects.

Claim 120 is commensurate in scope with the specification as originally filed at, for example, page 2, lines 4-6, page 17, line 3 to page 19, line 3, and in the working examples. The

invention teaches that the combination of chemotherapeutic agent and immunoconjugate produces unexpectedly superior results, and the working examples support the teachings in the specification. In support thereof, Applicant also previously submitted a Declaration under 37 CFR § 1.132 by Dr. Walter Blättler ("the Blättler Declaration" attached as Exhibit E to the Response filed May 5, 2004).

Dr. Blättler has declared that one skilled in the art would have expected that huN901 and huC242 in Examples 2-7 could have been substituted with other monoclonal antibodies that bind antigens expressed by cancer cells and that the same or substantially the same synergistic results would have been achieved. Dr. Blättler has also declared that one skilled in the art would have expected that one or more of paclitaxel, cisplatin, etoposide, docetaxel, topotecan, and irinotecan in Examples 2-7 could have been substituted with other chemotherapeutic agents and that the same or substantially the same synergistic results would have been achieved.

The PTO does not find the Blättler Declaration persuasive – after agreeing that combinations targeting CD56 and CanAg wherein the toxin portion of the immunoconjugate is maytansinoid (as shown in Examples 2-7) would not be expected to be synergistic, the PTO asserts that "[b]ecause synergism is an unexpected result, it would not be obvious that immunoconjugates targeting other cancer antigens in combination with other drugs would expect [sic] to be synergistic and further this is not relevant to the instant claims which do not require a synergistic effect between the chemotherapeutic agent and the immunoconjugate."[1] Applicant respectfully disagrees because one of skill in the art would expect that agents with the same or similar modes of action will achieve the same or substantially the same results; e.g. chemotherapeutic agents with the same or similar mode of action as the chemotherapeutic agents in Examples 2-7 and monoclonal antibodies with the same or similar mode of action as the monoclonal antibodies in Examples 2-7 may be substituted for the chemotherapeutic agents and monoclonal antibodies, respectively, of Examples 2-7 and one of skill in the art will expect the same or substantially the same results.

As to the PTO's argument that Dr. Blättler's declarations are not relevant to the instant claims which do not require a synergistic effect between the chemotherapeutic agent and the

[1] Office Action dated August 13, 2004, at pages 15-16.

immunoconjugate, Applicant submits that it is clear from the unexpectedly superior results shown in Examples 2-7 and the teachings in the specification that the invention is directed to synergistic combinations of a chemotherapeutic agent and an immunoconjugate.

The PTO also asserts that the working examples do not support a specific description of a genus of antibodies, which exert a synergistic therapeutic effect when administered with taxol. As the PTO's own examination guidelines state, for a claim drawn to a genus:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
> A representative number of species means that the species which are adequately described are representative of the entire genus... Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.
>
> (USPTO Guidelines for Examination of Patent Applications Under the 35 USC 112, 1, 'Written Description' Requirement. Official Gazette: Jan. 30, 2001)

Applicant has described a representative number of species in the specification as originally filed at, for example, page 17, line 3 to page 19, line 3, and in the working examples, to satisfy the statutory requirements for sufficient written description to support a genus of antibodies which exert a synergistic therapeutic effect when administered with taxol.

Based on the results in Examples 2-7, the teachings in the specification, the knowledge of one skilled in the art (e.g., that the chemotherapeutic agents in Examples 2-7 have the same or similar mode of action as other chemotherapeutic agents and that the monoclonal antibodies in Examples 2-7 have the same or similar mode of action as other monoclonal antibodies), and the Blättler Declaration, one skilled in the art would recognize that the pending claims are commensurate in scope with the specification as filed.

As the Examiner has correctly pointed out, Applicant has provided examples in support. The operative embodiments and the examples of the instant application meet the statutory guidelines of completeness and are of sufficient clarity to justify the scope of the claims. During

patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." MPEP 2111.

In view thereof, Applicant respectfully requests that this rejection be withdrawn.

III. First Rejection under 35 U.S.C. § 103 and Obviousness-Type Double Patenting Rejection

Claims 93-97, 99, 102-110, 112, 115-119 are rejected under 35 U.S.C. § 103(a) over Siegall et al, *Proc Annu Meet Am Assoc Cancer Res*, 38:A185 (1997) in view of Chari et al, *Cancer Research*, 52:127-131 (1992).

Claims 93-97, 99, 102-110, 112 and 115-119 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-12 of US Patent No. 5,208,020 in view of Siegall et al, *Proc. Annu. Meet Am. Assoc. Cancer Res.*, 38:A185 (1997) and Chari et al, *Cancer Research*, 52:127-131 (1992).

Applicant respectfully traverses the rejections and respectfully submits that the presently claimed invention is unobvious over the combination of cited references.

Siegall is wholly unrelated to the presently claimed invention. Siegall describes an immunoconjugate containing a monoclonal antibody bound to a truncated form of Pseudomonas exotoxin. *See* Friedman et al, *Cancer Research*, 53(2):334-339 (1993), attached as Exhibit F to the Response filed May 5, 2004. The PTO has not established any relationship between the immunoconjugate in Siegall, which contains a truncated form of Pseudomonas exotoxin, and the presently claimed immunoconjugate which comprises a maytansinoid.

The PTO asserts that "[o]ne of skill in the art would recognize that both PE40 and maytansin are protein toxins which would act catalytically when internalized by a cell, thus one of skill in the art would expect that a BR96-sFv-maytansinoid immunotoxin would have a similar therapeutic potential as the Br96-sFc-Pe40 immunotoxin."[2] The PTO's assertion is factually incorrect. PE40 is a catalytically active bacterial protein toxin that kills cells by ADP-ribosylation of elongation factor 2 (Pastan et al, *J. Biol. Chem.*, 264:15157-15160 (1989), attached as Exhibit H to the Response filed May 5, 2004). Maytansine is an antibiotic originally isolated from an African shrub and is chemically an ansamacrolide or polyketide. (Kupchan et al, *J. Am. Chem. Soc.*, 94: 1354-1356 (1972), attached as Exhibit I to the Response filed May 5,

[2] Office Action at page 5.

2004). Maytansinoids are antimitotic agents that bind to the intracellular protein tubulin and inhibit its polymerization to form microtubules. The claimed maytansinoids are not enzymes (i.e., like PE40) nor do they act catalytically in any other fashion (i.e., like PE40). Accordingly, Siegall, which teaches immunoconjugates comprising PE40, is wholly unrelated to the presently claimed invention.

The Examiner has applied *per se* assumptions to determine that the claims are obvious. The Examiner should note that the use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 USC § 103. See, e.g., *In re Brouwer*, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996). The Examiner is also reminded that a determination of patentability under 35 USC § 103 should be made upon the facts of the particular case in view of the totality of the circumstances. See, e.g., *In re Dillon*, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)(en banc), cert. denied, 500 US 904 (1991).

With respect to the obviousness type double patenting rejection, the Examiner is reminded that in determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is: does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent? A comparison of the claims of the Chari patent and the instant application in light of the disclosure made in the specification clearly establishes that the claims of the instant application are materially different from the Chari patent because the instant application teaches and claims a composition comprising a combination of one or more chemotherapeutic drugs and an immunoconjugate and that a composition comprising such a combination functions synergistically in modulating cell proliferation.

Because the basis for the PTO's rejections are factually incorrect, Siegall does not properly form a basis to reject the present claims. Without Siegall, the rejections cannot be maintained. Accordingly, the rejection under 35 USC § 103 and the obviousness type double patenting rejection must be withdrawn.

IV. Second and Fourth Rejections under 35 USC § 103

(Second Rejection): Claims 93-97, 99, 101-110, 112, 114-119, 144, 146, 148 and 150 are rejected under 35 USC § 103 as being obvious over Liu, *Expert Opinion on Investigational*

Drugs, 6:169-172 (1997) in view of Iwasaki et al, *Yakugaku Zasshi*, 118:111-126 (1998) and Pegram et al, *Oncogene*, 18:2241-2251 (1999) and Watson et al, *Proc Annu Meet Am Assoc Cancer Res*, 37:A2997 (1996) and Schlom (Monoclonal Antibodies: They're More and Less Thank You Think, *Molecular Foundations of Oncology*, 1991, Ed. S. Broder, pp. 95-134).

(Fourth Rejection): Claims 93-98, 100-111, 113, 115-119 are rejected under 35 U.S.C. § 103(a) as being obvious over Guchelaar et al, *Clinical Oncology*, 6:40-48 (1994) in view of Liu et al, *Proc Annu Meet Am Assoc Cancer Res*, 38:A190 (1997) and Lynch et al, *Journal of Clinical Oncology*, 15:723-734 (1997) and Liu *Expert Opinion on Investigational Drugs*, 6:169-172 (1997) and Iwasaki et al, *Yakugaku Zasshi*, 118:111-126 (1998) and Pegram et al, *Oncogene*, 18:2241-2251 (1999).

Applicant respectfully traverses the rejections and respectfully submits that the presently claimed invention is unobvious over the combination of cited references. After summarizing and analyzing the references, the PTO concludes the second and fourth obviousness rejections with the following statement:

> Because the mechanisms of action of these two agents differ with respect to the molecular basis by which they induce an anti-mitotic effect, it is logical to suppose that the combination of the two agents might produce some additive effect.[3]

Contrary to this statement, the data in the specification demonstrates that the combination of the claimed immunoconjugate and chemotherapeutic agent produce synergistic (i.e., more than additive) effects. As admitted by the PTO, it would be logical to suppose that the two "might produce some additive effect." Accordingly, it would be completely unexpected that the two would produce more than an additive effect (i.e., a synergistic effect). This is Applicant's basis for overcoming the obviousness rejections.

The data in the specification shows that the presently claimed compositions/kits provide superior (i.e., greater than additive, synergistic) results that would be unexpected in view of the teachings in the cited references and the statements made by the PTO.[4] For the Examiner's convenience, a summary of the data in the specification is shown below.

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[3] Office Action at page 8, lines 23-25, and page 11, lines 16-18.
[4] Office Action at page 8, lines 23-25, and page 11, lines 16-18.

	Treatment Groups	Therapeutic agents	Results
Example 2	Control	Untreated	Tumors grew rapidly to a size of about 900 mm^3 by day 28 post-tumor inoculation
	Group 1	huN901-DM1	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 2	Paclitaxel	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 3	huN901-DM1 and paclitaxel	Tumors disappeared with complete regression lasting 58 days
Example 3	Control	Untreated	Tumors grew rapidly to a size of about 900 mm^3 by day 28 post-tumor inoculation
	Group 1	huN901-DM1	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 2	cisplatin and etoposide	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 3	huN901-DM1 and cisplatin and etoposide	Tumor growth delay of 12 days (50% longer than what one would expect for an additive anti-tumor effect)
Example 4	Control	Phosphate buffered saline	Tumor grew rapidly to about 1000 mm^3 in 26 days
	Group 1	Docetaxel	Tumor growth delay of 8 days
	Group 2	huN901-DM1	Tumor growth delay of 20 days
	Group 3	Docetaxel and huN901-DM1	Complete tumor regression in all animals. In 3 out of 6 animals tumor was eradicated resulting in cures lasting greater than 200 days. In remaining 3 animals, tumor growth delay of 52 days (24 days longer than calculated additive effect).
Example 5	Control	Phosphate-buffered saline	Tumors grew to about 800 mm^3 in 44 days
	Group 1	Topotecan	Tumor growth delays of 12 days
	Group 2	huN901-DM1	Tumor growth delay of 34 days in 3out of 6 animals. Remaining 3 animals had complete tumor regression
	Group 3	Topotecan and huN901-DM1	Complete tumor regression in 5 out of 6 animals and tumor-free on day 78

Example 6	Control	Phosphate-buffered saline	Tumors grew rapidly to about 1000 mm^3 in 32 days
	Group 1	Paclitaxel	Tumor growth delay of 4 days
	Group 2	huC242-DM1	Shrinkage of tumor, but none of the 6 treated animals showed complete tumor regression
	Group 3	Paclitaxel and huC242-DM1	Showed greater anti-tumor effect resulting in complete tumor regression, with 3 out of 6 animals showing no evidence of tumor. The remaining 3 animals showed significant shrinkage in tumor.
Example 7	Control	Phosphate-buffered saline	Tumors grew rapidly to about 1000 mm^3 in 31 days
	Group 1	CPT-11 (i.e., irinotecan)	Tumor growth delay of 6 days
	Group 2	C242-DM1	Delay in tumor growth of 22 days
	Group 3	CPT-11 (i.e., irinotecan) and C242-DM1	Tumor growth delay of 38 days (10 days longer than calculated additive effect)

Applicant respectfully submits that the unexpectedly superior results shown in Examples 2-7 in the specification successfully rebut the obviousness rejection set forth by the Patent Office. As MPEP § 716.02(a) states:

SUPERIORITY OF A PROPERTY SHARED WITH THE PRIOR ART IS EVIDENCE OF NONOBVIOUSNESS

> Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties ... can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective than the closest prior art compound in controlling quackgrass and yellow nutsedge weeds in corn and soybean crops was sufficient to overcome the rejection under 35 U.S.C. 103, even though the specification indicated the claimed compound was an average performer on crops other than corn and soybean.). See also *Ex parte A*, 17 USPQ2d 1716 (Bd. Pt. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut *prima facie* obviousness even though there was no evidence that the compound was effective against all bacteria.)

The MPEP states that evidence of unexpectedly superior results is sufficient to obtain patent protection for claims directed to a compound or composition. In other words, a showing of unexpectedly superior results does not merely confer patentability to the methods of use — it also confers patentability to the compositions.

The PTO asserts that the motivation for combining the individual references rests on the fact that the combination would be expected to be "non-antagonistic" and therefore additive to some degree. However, as previously discussed, the present invention is directed to compositions and kits comprising synergistic (i.e. more than additive) combinations of a chemotherapeutic agent and an immunoconjugate. None of the combinations of references cited by the Examiner teach or suggest synergistic combinations of a chemotherapeutic agent and an immunoconjugate.

The Examiner has applied *per se* assumptions to determine that the claims are obvious. The Examiner should note that the use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 USC § 103. See, e.g., *In re Brouwer*, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996). The Examiner is also reminded that a determination of patentability under 35 USC § 103 should be made upon the facts of the particular case in view of the totality of the circumstances. See, e.g., *In re Dillon*, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)(en banc), cert. denied, 500 US 904 (1991).

In view of the above, Applicant respectfully submits that the claims are unobvious over the cited references and respectfully request that the rejections under 35 USC § 103 be withdrawn.

V. Third Rejection under 35 USC § 103

Claims 93-97, 99, 101-110, 112, 114-119 and 144-151 are rejected under 35 USC § 103 as being obvious over Liu, *Expert Opinion on Investigational Drugs*, 6:169-172 (1997) in view of Iwasaki et al, *Yakugaku Zasshi*, 118:111-126 (1998) and Pegram et al, *Oncogene*, 18:2241-2251 (1999) and Watson et al, *Proc Annu Meet Am Assoc Cancer Res*, 37:A2997 (1996) and Schlom (Monoclonal Antibodies: They're More and Less Thank You Think, *Molecular Foundations of Oncology*, 1991, Ed. S. Broder, pp. 95-134) and further in view of Chari et al, *Cancer Research*, 52:127-131 (1992).

Applicant respectfully traverses this rejection. As previously discussed in Part IV above (which is incorporated by reference in its entirety), the combination of Liu, Iwasaki, Pegram, Watson and Schlom does not teach or suggest synergistic combinations of a chemotherapeutic agent and an immunoconjugate. The addition of Chari does not cure the deficiencies of these other references and does not change that the presently claimed invention provides unexpectedly superior results when compared to the prior art.

The Examiner has applied *per se* assumptions to determine that the claims are obvious. The Examiner should note that the use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 USC § 103. See, e.g., *In re Brouwer*, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996). The Examiner is also reminded that a determination of patentability under 35 USC § 103 should be made upon the facts of the particular case in view of the totality of the circumstances. See, e.g., *In re Dillon*, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)(en banc), cert. denied, 500 US 904 (1991).

In view thereof, Applicant respectfully requests that this obviousness rejection be withdrawn.

VI. Fifth Rejection under 35 USC § 103

Claims 93-113 and 115-119 are rejected under 35 U.S.C. § 103(a) as being obvious over Guchelaar et al, *Clinical Oncology*, 6:40-48 (1994) in view of Liu et al, *Proc Annu Meet Am Assoc Cancer Res*, 38:A190 (1997) and Liu, *Expert Opinion on Investigational Drugs*, 6:169-172 (1997) and Iwasaki et al, *Yakugaku Zasshi*, 118:111-126 (1998) and Pegram et al, *Oncogene*, 18:2241-2251 (1999) and further in view of Schlom, *Molecular Foundations of Oncology*, Ed. S. Broder, pages 95-134 (1991).

Applicant respectfully traverses the rejection. Because claims 93-113 and 115-119 are unobvious over Guchelaar, Liu, Iwasaki and Pegram for the reasons discussed in Part IV above (which is incorporated by reference in its entirety), claims 93-113 and 115-119 are also unobvious over Guchelaar, Liu, Iwasaki, and Pegram and further in view of Schlom. Schlom does not cure the deficiencies of the other references and does not change that the presently claimed invention provides unexpectedly superior results when compared to the prior art.

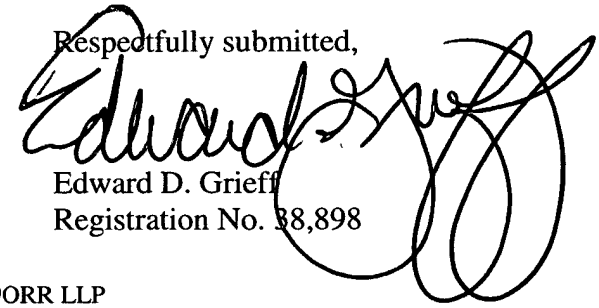
The Examiner has applied *per se* assumptions to determine that the claims are obvious. The Examiner should note that the use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 USC § 103. See, e.g., *In re Brouwer*, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996). The Examiner is also reminded that a determination of patentability under 35 USC § 103 should be made upon the facts of the particular case in view of the totality of the circumstances. See, e.g., *In re Dillon*, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)(en banc), cert. denied, 500 US 904 (1991).

In view of the above, Applicant respectfully requests that this obviousness rejection be withdrawn.

VII. Conclusion

Applicant respectfully requests an early and favorable reconsideration and allowance of pending claims 105-120 and 144-163. The Examiner is encouraged to telephone the undersigned to expedite prosecution of this application.

Respectfully submitted,



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